REMARKS

I. Introduction

Receipt is acknowledged of a non-final office action dated August 12, 2004. In the action, the examiner rejected claims 3-7 as allegedly indefinite, claims 1-19 as allegedly lacking written description, claims 1-3, 6-7, 9-14, 17, 18 and 20 as obvious over Pinto *et al.* (*Prostate J.*, 1:15-26 (1999) in view of Julian *et al.* (U.S. 5,717,064), and also claims 1-7, 9-18 and 20-23 further in view of Leippe *et al.* (*PNAS*, 91:2602-2606 (1994). Lastly, the examiner objected to claims 5, 7, 8, 16, 18, 19 and 22 for formality reasons.

II. Status of the Claims

In this response, applicants amended claims 3, 5, 7, 8, 16, 18, 19, 22 and 23, and added new claims 24-26. Support for the amended claims can be found in originally filed claims 5, 7, 8, 16, 18 and 19, and on pages 9 and 12 of the instant specification. Support for new claim 24 can be found in originally filed claim 19. Support for new claims 25 and 26 can be found throughout the specification, and on pages 23-24 in particular.

Applicants wish to point out that in a response filed on May 18, 2004, applicants inadvertently listed claims which did not take applicants' June 20, 2002 amendment into account. The claims amended in the June 20th response were revised to recite SEQ ID numbers (claims 5, 7, 8, 16, 18 and 19), as well as to correct the amoebapore sequence recited in claims 8 and 19 (a leucine residue was omitted from the claims (support for which can be found in Table 1, on page 9 of the specification) and COOH was changed to $CONH_2$ (support for which can be found on page 12 in the structure of the procytolytic peptide)). The sequence listing filed on August 27, 2002 has these changes accounted for and is correct.

Therefore, applicants have reintroduced these amendments in the present response.

Applicants also wish to point out that the examiner indicated in her August 12, 2004 office action that claims 8 and 19 would be allowable if rewritten in independent form. However, applicants realized that claim 19 was improperly dependent on claim 17 and should have been dependent on claim 14 (which is apparent from the claims themselves). So in order to avoid confusion, applicants separated the species recited in the Markush group in claim 19, and amended the claim to be in independent form and read only on the melittin sequence (instead of melittin and amoebapore). Accordingly, reference to the amoebapore sequence was removed from claim 19 and instead added as a new claim – claim 24. New claim 24 therefore now recites the same features as claim 19 except is directed only to amoebapore.

Thus, upon entry of this amendment, claims 1-26 will be under examination.

III. Claim Objections

In the action the examiner objected to claims 5, 7, 8, 16, 18, 19 and 22 for lacking sequence compliance. Office action at 2. Accordingly, applicants inserted a sequence identifier following the amino acid sequence(s) recited in the claims. Applicants trust that these amendments address the examiner's concerns.

IV. Rejection under 35 U.S.C. § 112, 2nd Paragraph

The examiner also rejected claims 3-7 as allegedly indefinite. In particular, the examiner stated it is unclear if the phrase "derivatives thereof" are derivatives of the individual recited species or if they refer only to "analogs thereof." Applicants amended claim 3 to recite "analogs of the pore-forming cytolytic peptide and derivatives of the pore-forming cytolytic peptide." Applicants trust that this amendment more clearly defines the present invention.

Support for this amendment can be found in paragraph 0028, on page 10 of the present specification.

In addition, the examiner asserted that "the metes and bounds of a[n] 'analog' and 'derivative'...cannot be determined with exactitude as attributes of an 'analog' and 'derivative' are not defined by the specification." Office action at 2. Applicants respectfully disagree.

The present specification describes that analogs and derivatives of the cytolytic peptides of the present invention retain their cytolytic activity when in the active conformation. Specifically, the instant application teaches that "[m]odification and derivatization according to the instant invention include, but are not limited to substitutions, additions or deletions *that provide for functionally equivalent molecules.*" Paragraph 30 at 11. As discussed below, the working examples in the present specification detail how function of the cytolytic peptide analogs and derivatives can be assessed.

V. Rejection under 35 U.S.C. § 112, 1st paragraph

The examiner rejected claims 1-19 for allegedly failing to comply with the written description requirement. In particular, the examiner stated that "[t]he specification does not provide examples of a representative number of species which fall within the bounds of each of the genuses." Office action at 3.

Applicants respectfully assert that the present specification discloses modifying and derivatizing cytolytic peptides. In fact, the present application provides examples of the types of analogs and derivatives contemplated in the present invention, and those for amoebapore in particular. Paragraph 0031 on pages 11-12 of the specification. Additionally, conservative amino acid substitutions are well known in the art and therefore, structural changes can be made to a cytolytic peptide without destroying function. Function of the analogs and derivatives of the cytolytic peptides can then be assessed according to, for example, Examples 2 and 3 as provided in the specification.

Further, the specification incorporates by reference a publication which discloses shortened amoebapore analogs with enhanced antibacterial and cytolytic activities. Paragraph 0028 at 20 of the instant specification. Also, the application discloses that dimerization, truncation, diastereoisomers and combinations thereof can be used for producing derivatives and analogs. Paragraph 0032 at 12.

Indeed, the examiner stated that "Julian et al teach that previous studies have indicated that replacement of amino acid residues within a helix may be carried out without substantial loss of activity as long as the segregation of polar and apolar residues on opposing faces of the helix us [*sic*] is preserved...thus fulfilling the specific embodiments of analogs and derivatives of melittin, magainin and amoebapore." Office action at 6. Additionally, the examiner asserted that a skilled artisan "would also understand that amino acid substitution on lytic peptides comprising α-helices can be carried out." Id.

Thus, one of skill in the art would know, based on the teachings of the present specification and the state of the art, what is meant by analogs and derivatives, and examples of such (eg, a cytolytic peptide with conservative amino acid substitutions). Accordingly, analogs and derivatives of amoebapore, melittin and other cytolytic peptides satisfy the written description requirement.

VI. Rejection under 35 U.S.C. § 103

The examiner rejected claims 1-3, 6-7, 9-14, 17, 18 and 20 as allegedly obvious over Pinto, in view of Julian. Specifically, the examiner asserted that a skilled artisan "would be motivated to temporarily neutralize the overall positive charge of the lytic peptides in order that said lytic peptides would not exert a proliferative or toxic effect on normal cells" and that "when in the vicinity of prostate cancer cells expressing PSMA,...the positive charge density w[ould] be restored to the lytic peptide." Office action at 5. Applicants respectfully disagree.

To establish a prima facie case of obviousness, there must be (1) some suggestion or motivation to modify the reference or to combine reference teachings, (2) a reasonable expectation of success, and (3) that the prior art references, when combined, teach or suggest all the claim limitations to establish a *prima facie* case of obviousness. *See* MPEP §2143 (Aug. 2001). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants respectfully assert that the examiner has not met her burden.

In the action, the examiner stated that Pinto "teach strategies which employ intravenous administration of poly-γ-glutamated drugs is a promising approach that would maximize toxicity to cells expressing PSMA..." but that Pinto "do[es] not specifically teach lytic peptides as drugs." Office action at 4.

The examiner then alleged that the deficiencies in Pinto are taught in Julian. In particular, the examiner contended that "Julian et al teach that amphipathy alone does not provide for lytic action and it is necessary to have an overall positive charge density for lytic activity" and that "modification of the ε-amino groups by methylation...maintains the lytic activity since the overall charge density is not altered by methylation." Office action at 5.

As described in applicants last response, Pinto reports that PSMA exhibits folate hydrolase activity and therefore, when methotrexate (MTX) is modified by adding gamma glutamates *to the end* of the molecule, PSMA sequentially removes these residues and permits MTX entry into the cell. However, this reference is different from the present invention in the following ways: (1) MTX and lytic peptides (a) vary significantly in size, (b) fall within different classes of compounds, and (c) have distinctly different modes of action (MTX acts intracellularly and lytic peptides act on the surface of a target cell to form holes in a cell membrane); (2) simply adding gamma glutamate residues to the end of a cytolytic peptide would not necessarily render the peptide inactive, and (3)

the modification to the claimed procytotoxin has to be between the ε-amino group of at least one lysine residue and at least one amino acid. These differences are not taught in Julian.

Julian teaches methylation of synthetic lytic peptide compositions to ***enhance resistance to proteolytic digestion***, thereby prolonging the life of the peptide. Applicants respectfully assert that a skilled artisan would not be motivated to combine the teachings of Pinto with Julian to derive the present invention.

As briefly discussed, Julian describes enhancing the effectiveness of a lytic peptide by rendering it less susceptible to tryptic digestion. On the other hand, the present invention discloses modifying a peptide to ***inactivate*** it, not make it more resilient to proteases and promote lytic activity. Thus, Julian teaches away from modifying a lytic peptide so as to decrease its lytic activity; in fact, Julian teaches just the opposite.

Moreover, Julian has a 1998 publication date and Pinto was published in 1999. If it would have been so obvious for one of skill in the art to "temporarily neutralize the overall positive charge of the lytic peptides in order that said lytic peptides would not exert a proliferative or toxic effect on normal cells" and that a skilled artisan would do so by "modify[ing] the ε-amino groups of melittin...by adding Glu residues," then one would expect that such a composition would be described in the literature by this time, five years post-Pinto. However, to the best of applicants' knowledge, such a procytotoxin has not been described to date other than in the present application.

Continuing, the examiner rejected claims 1-7, 9-18 and 20-23 as obvious over Pinto and Julian, and further in view of Leippe. In particular, the examiner stated that in view of Pinto and Julian, and based on the teachings of Leippe "on the properties of amoebapore versus melittin" that "it would have been prima facie obvious...to substitute amoebapore for melittin in the method of treating prostate cancer." Office action at 6. Applicants respectfully assert that for the

reasons discussed above, the deficiencies in the teachings of Leippe are not addressed by the Pinto and Julian references. Therefore, the claimed invention is not obvious over the cited art.

CONCLUSION

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and arguments.

It is respectfully urged that the present application is now in condition for allowance. Early notice to that effect is earnestly solicited.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date September 13, 2004

By _____

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